Tumour exosome integrins determine organotropic metastasis.

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Public Summary:

Scientific Abstract:
Ever since Stephen Paget's 1889 hypothesis, metastatic organotropism has remained one of cancer's greatest mysteries. Here we demonstrate that exosomes from mouse and human lung-, liver- and brain-tropic tumour cells fuse preferentially with resident cells at their predicted destination, namely lung fibroblasts and epithelial cells, liver Kupffer cells and brain endothelial cells. We show that tumour-derived exosomes uptaken by organ-specific cells prepare the pre-metastatic niche. Treatment with exosomes from lung-tropic models redirected the metastasis of bone-tropic tumour cells. Exosome proteomics revealed distinct integrin expression patterns, in which the exosomal integrins alpha6beta4 and alpha6beta1 were associated with lung metastasis, while exosomal integrin alphavbeta5 was linked to liver metastasis. Targeting the integrins alpha6beta4 and alphavbeta5 decreased exosome uptake, as well as lung and liver metastasis, respectively. We demonstrate that exosome integrin uptake by resident cells activates Src phosphorylation and pro-inflammatory S100 gene expression. Finally, our clinical data indicate that exosomal integrins could be used to predict organ-specific metastasis.